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Retinal Ganglion Cells and Circadian Rhythms in Alzheimer's Disease, Parkinson's Disease, and Beyond

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There is increasing awareness on the role played by circadian rhythm abnormalities in neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD). The characterization of the circadian dysfunction parallels the mounting evidence that the hallmarks of neurodegeneration also affect the retina and frequently lead to loss of retinal ganglion cells (RGCs) and to different degrees of optic neuropathy. In the RGC population, there is the subgroup of cells intrinsically photosensitive and expressing the photopigment melanopsin [melanopsin-containing retinal ganglion cells (mRGCs)], which are now well known to drive the entrainment of circadian rhythms to the light–dark cycles. Thus, the correlation between the pathological changes affecting the retina and mRGCs with the circadian imbalance in these neurodegenerative diseases is now clearly emerging, pointing to the possibility that these patients might be amenable to and benefit from light therapy. Currently, this connection is better established for AD and PD, but the same scenario may apply to other neurodegenerative disorders, such as Huntington's disease. This review highlights similarities and differences in the retinal/circadian rhythm axis in these neurodegenerative diseases posing a working frame for future studies.

Keywords: optic nerve, retinal ganglion cells, melanopsin, circadian rhythms, Parkinson's disease, Alzheimer's disease, Huntington's disease

INTRODUCTION

Alzheimer's disease (AD) and Parkinson's disease (PD) are the most frequent age-related neurodegenerative disorders with an increasing prevalence with age (1, 2). They are both characterized by the frequent occurrence of sleep problems and circadian rhythm dysfunction (3–6). In the last decade, the role of the eye in influencing and regulating circadian rhythms has been clarified, starting from the discovery of the intrinsically photosensitive melanopsin-containing retinal ganglion cells (mRGCs) (7, 8). These cells constitute a small subset of regular retinal ganglion cells (RGCs) consisting of about 1–2% of the total, and they give origin to the retinohypothalamic tract through which they project to the suprachiasmatic nucleus (SCN) of the hypothalamus synchronizing circadian rhythms to the light–dark cycle (9). Besides this predominant function, they also play an important role in many non-visual functions of the eye, regulating sleep through the connections with the ventrolateral preoptic nucleus (VLPO) and the lateral hypothalamus (LH), melatonin secretion, and its suppression through the connections with the pineal gland, pupillary reflex through the olivary

pretectal nucleus, and also visual functions through the projection to the lateral geniculate nucleus (10–12).

In this review, the likely influence of the mRGC system in the pathogenesis of circadian misalignment in AD and PD is discussed, highlighting similarities and differences, starting from the observation that in both diseases, loss of regular RGCs has been documented by both histological and optical coherence tomography (OCT) studies, thus suggesting that the retina is actively and primarily involved in the neurodegenerative process characterizing both disorders. In fact, many studies describe optic neuropathies associated with AD and PD, which, however, display different patterns of RGC and axonal loss, possibly reflecting different pathogenic mechanisms. We here explore the connection between the eye and circadian functions and dysfunctions in AD and PD with particular reference to the mRGC system and its contribution to circadian functions.

EVIDENCE OF INNER RETINA PATHOLOGY IN AD AND PD

Alzheimer's Disease

Histological and OCT studies in AD demonstrated a significant loss of RGCs and consequent axonal depletion in the optic nerve. Hinton and colleagues in 1986 reported the first histological demonstration of optic neuropathy in AD describing loss of RGCs and axons in the optic nerve (13). After this seminal work, other histological studies reported degeneration of the inner retina in AD, more pronounced in the superior and inferior sectors of the optic nerve (14–20).

These histological findings are corroborated by many recent OCT studies pointing to retinal nerve fiber layer (RNFL) thinning in AD, as confirmed by a recent meta-analysis of 11 OCT studies in AD (21). RNFL thinning is more pronounced in the superior sector of the optic nerve (20–23) and is age related (20) (**Figure 1**). This pattern of RGC loss is consistent with the predominant inferior visual field defect described in AD patients (24). Moreover, a recent OCT study using segmentation analysis in a large series of AD patients showed a significantly reduced macular retinal ganglion cell–inner plexiform layer thickness in AD retinas compared to controls (25).

The pattern of axonal loss in the optic nerve, for example, the prominent superior quadrant involvement, is consistent with the histological findings that magnocellular RGCs are more vulnerable to AD pathology (16), which also resembles the pattern of RGC loss described in glaucoma (26). Recently developed *in vivo* imaging methods, such as the detection of retinal cells undergoing apoptosis (DARC), are extremely promising in quantifying and visualizing *in vivo* RGC loss in AD retinas (27).

The presence of the cerebral hallmarks of AD, such as amyloid plaques, in the retina gives strength to the specific vulnerability of the eye, and in particular of the inner retina to AD pathology. Koronyo-Hamaoui and colleagues provided the first demonstration of extra-cerebral A β deposits in postmortem human flat-mounted retinas of AD patients and *ex vivo* in APPSWE/PS1 Δ E9 transgenic mice after curcumin administration (28). Subsequent studies confirmed the presence of specific amyloid

pathology, including both extracellular plaques and intracellular A β deposits, more evident in the superior quadrant, and increased A β peptides levels in human AD retinas (20, 29, 30) (**Figure 1**). Other promising imaging techniques, recently developed for visualizing amyloid deposits in AD retinas, include hyperspectral imaging (31), the use of cross-polarizers (32), and the polarization-sensitive OCT (33). Schön and coauthors also demonstrated the presence of the other hallmark of AD pathology, such as the phosphorylated tau, in human AD retinas (34).

Finally, our group recently demonstrated that a specific subpopulation of RGCs, the mRGCs, are specifically lost in AD and affected by the amyloid pathology. In fact, using melanopsin and A β co-staining, our group showed that A β deposits are evident within and around these cells affecting also mRGC neuritis (20). Remarkably, the loss of these cells is evident even with a normal RGC count, pointing to a specific AD pathology affecting mRGCs (20). The loss of these cells is particularly relevant for interpreting the occurrence of sleep and circadian disturbances in AD (see next section).

Parkinson's Disease

The occurrence of visual problems is a frequent finding in PD patients. These include blink, dry eyes, reduced visual acuity, contrast sensitivity, color vision abnormalities, oculomotor disturbances, and visual hallucinations (35, 36).

In particular, contrast sensitivity abnormalities are related to dopamine depletion at the retina levels (37–39) and can be partially reversed by the administration of L-DOPA therapy in PD patients (40). In fact, dopaminergic amacrine cells in the retina regulate the center-surround organization of RGC receptive fields and their dysfunction leads the retina to be in an inappropriately dark-adapted state (35). Color vision in PD patients is an early sign involving, at difference with the color defects observed with aging, the protan–deutan axis (red–green) (41). Interestingly, color vision abnormalities have good discriminative power in distinguishing PD patients from controls in the early stage of disease and may predict the conversion of idiopathic REM behavior disorder patients to PD (42, 43). However, the Farnsworth–Munsell 100 Hue test, commonly used for testing color abilities in PD, is influenced also by cognitive functions such as executive functions, and this must be taken into account in the interpretation of these results.

Besides the retinal dopaminergic depletion, which explains the occurrence of contrast sensitivity abnormalities in PD, there are multiple evidences pointing to RGC loss in PD (44, 45) (**Figure 1**). The presence of optic neuropathy has been reported by many OCT studies and, interestingly, the pattern of axonal loss resembles that typically seen in mitochondrial optic neuropathies, affecting the temporal sector of the optic nerve, i.e., the papillomacular bundle (RGC) (44, 46, 47). This pattern of RGC loss, which affects predominantly the parvocellular component, is clearly distinguishable from that described in AD, for which more frequently the magnocellular RGCs are affected (16, 20, 21) and other Parkinsonian syndromes, such as multiple system atrophy (**Figure 1**) (48).

Moreover, the optic neuropathy in PD is more pronounced in the eye contralateral to the most affected body side (46), suggesting a congruent asymmetry of the neurodegenerative process affecting

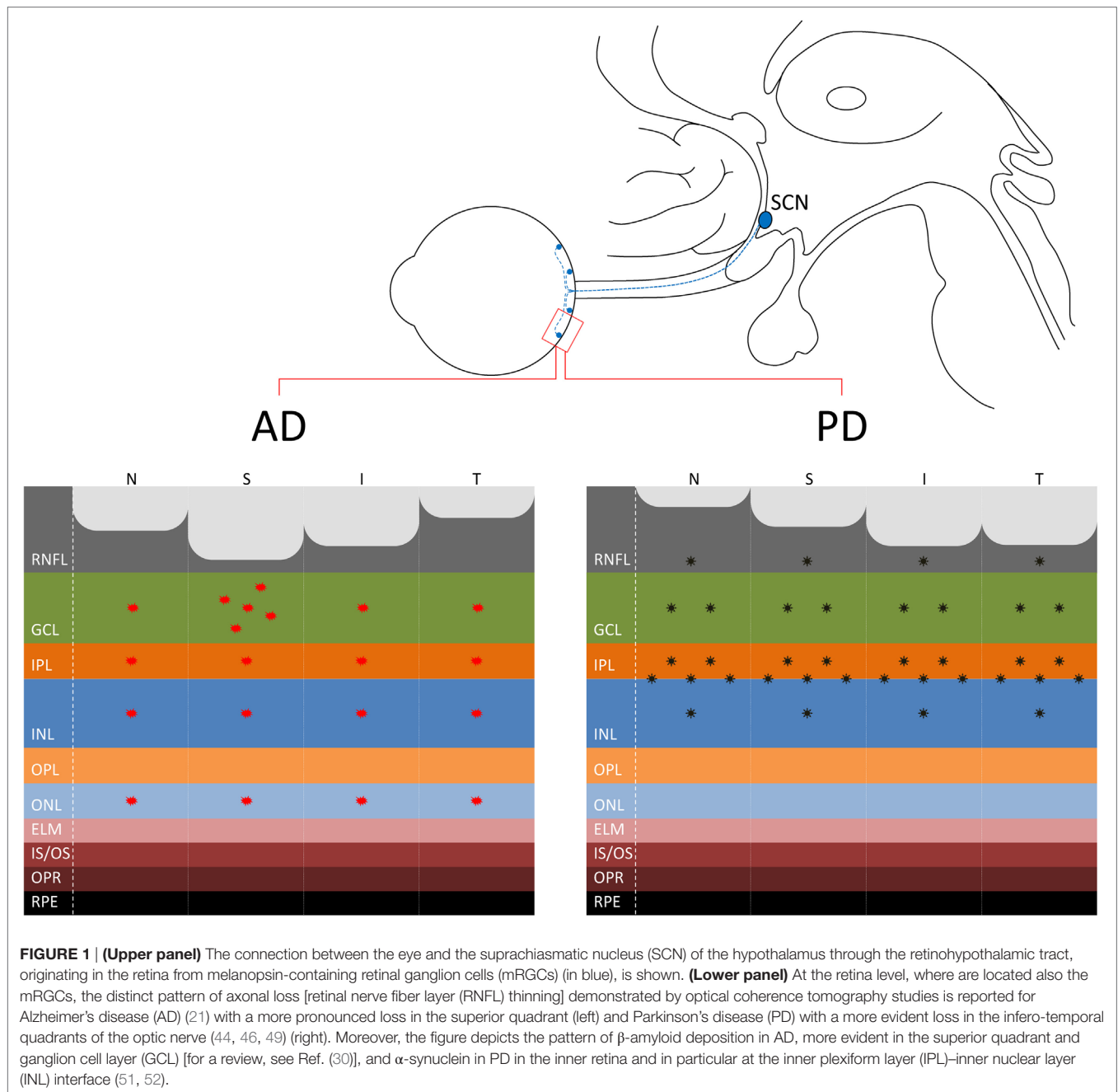


FIGURE 1 | (Upper panel) The connection between the eye and the suprachiasmatic nucleus (SCN) of the hypothalamus through the retinohypothalamic tract, originating in the retina from melanopsin-containing retinal ganglion cells (mRGCs) (in blue), is shown. **(Lower panel)** At the retina level, where are located also the mRGCs, the distinct pattern of axonal loss [retinal nerve fiber layer (RNFL) thinning] demonstrated by optical coherence tomography studies is reported for Alzheimer's disease (AD) (21) with a more pronounced loss in the superior quadrant (left) and Parkinson's disease (PD) with a more evident loss in the infero-temporal quadrants of the optic nerve (44, 46, 49) (right). Moreover, the figure depicts the pattern of β -amyloid deposition in AD, more evident in the superior quadrant and ganglion cell layer (GCL) [for a review, see Ref. (30)], and α -synuclein in PD in the inner retina and in particular at the inner plexiform layer (IPL)–inner nuclear layer (INL) interface (51, 52).

also the retina. This asymmetry has been also documented for the foveal remodeling demonstrated in PD patients, as a hallmark of retinal pathology in PD (49, 50).

Finally, recent studies reported the presence of α -synuclein deposition in the retina of PD patients and in particular in the inner retina, pointing to a specific PD pathology affecting the eye (51, 52) (**Figure 1**). Interestingly, the staining of phosphorylated synuclein (p-syn) shown by Beach and colleagues (52) affected a large cell with an extensive dendritic tree, which resembles an mRGC. The possible occurrence of α -synuclein pathology affecting the mRGCs in PD may contribute to the occurrence of circadian dysfunction in PD that remains to be tested.

CIRCADIAN RHYTHM DYSFUNCTION IN AD AND PD

Alzheimer's Disease

Sleep and circadian disturbances are a frequent complaint of AD patients, appearing in the majority of cases early in the disease course and including daytime somnolence, increased sleep latency, and frequent night-time awakenings with sleep fragmentation (3). Some of the sleep changes described in AD are the same reported with aging, such as the reduction of slow wave sleep and the difficulty in sleep maintenance (53). Other sleep abnormalities, such as the reduction of REM sleep, are more specifically related to AD (54).

Circadian rhythm abnormalities are reported in AD patients even in the early stage of the disease including a delayed phase of the temperature rhythm (55), sundowning, i.e., the appearance of behavioral agitation in the evening (56), the reduction of melatonin levels during the night (57), and the circadian expression profile of clock genes (57, 58). Moreover, abnormalities of the rest–activity circadian rhythm, including increased intra-daily variability (IV) and reduced inter-daily stability (IS) and relative amplitude of the rest–activity rhythm are described in AD (59, 60), and the presence of circadian dysfunction may predict a poor outcome in terms of cognitive functions (59).

We recently demonstrated the presence of variable degrees of rest–activity circadian dysfunction in mild–moderate AD patients and a specific loss of mRGCs in AD retinas (20). A specific AD pathology affecting these cells may contribute to circadian dysfunction in AD patients. Moreover, these cells have a direct effect on sleep through direct and indirect projections to brain nuclei relevant for sleep regulation such as the LH and the VLPO (61, 62). The role of mRGC loss in contributing to sleep and circadian misalignment in AD is particularly relevant for its potential therapeutic options. In fact, the use of bright light therapy has been proven to be effective in counteracting sleep and circadian dysfunction in AD (63, 64).

Other possible components of the circadian imbalance demonstrated in AD is the presence of SCN neuronal loss and amyloid pathology documented in neuropathological studies of AD postmortem brain (65, 66), which correlates with the degree of rest–activity disruption (67) and can contribute secondarily to the mRGC loss demonstrated in AD retinas.

The strict relationship between cognition, sleep, and circadian rhythms is highlighted also by the demonstration that the presence of circadian dysfunction may predict the onset of dementia (68), as well as that sleep loss may promote the accumulation of amyloid and predispose to AD (53, 69). Many recent studies point to direct and indirect effects of circadian derangement in cognitive disturbances and hence dementia. Counteracting the circadian imbalance may have important clinical implications. A summary of circadian abnormalities in AD is reported in **Table 1**.

Parkinson's Disease

Sleep disturbances are reported in about 80% of PD patients (5). Furthermore, circadian dysfunction has been extensively described in PD patients, in terms of the following:

- (1) Abnormal melatonin rhythm, i.e., abnormal phase angle of melatonin rhythm (70, 71) and decreased amplitude (72, 73). However, the phase advance of the melatonin rhythm documented by these studies was evident only in L-DOPA-treated PD patients, suggesting a possible influence of medications on these findings.
- (2) Abnormal rest–activity rhythm, and in particular increased IV, reduced IS, and flattening of daily activity (74–76). However, a relevant influence of medications, motor, and non-motor symptoms (in particular cognitive disturbances and hallucinations) has been postulated also for these findings (6).
- (3) Abnormal blood pressure (BP) and heart rate (HR) rhythm abnormalities such as reversal of circadian BP rhythm and loss

TABLE 1 | Summary of circadian rhythm abnormalities in AD, PD, and HD.

| | Circadian rhythm abnormalities | Reference |
|----|--|-----------|
| AD | <ul style="list-style-type: none"> • Daytime somnolence, increased sleep latency, and night-time awakenings (3) • Delayed phase of temperature circadian rhythm (55) • Sundowning (56) • Reduction of night-time melatonin levels (57) • Abnormal circadian expression profile of clock genes (57, 58) • Increased IV, reduced IS, and reduced RA of rest–activity circadian rhythm (20, 59, 60, 67) | |
| PD | <ul style="list-style-type: none"> • Abnormal melatonin circadian rhythm (phase advance and decreased amplitude) (70–73) • Increased IV, reduced IS, and reduced RA of rest–activity circadian rhythm (74–76) • Reversal of circadian BP rhythm and loss of HR variability (77, 78) • Abnormal temperature and cortisol circadian rhythm (73, 80) • Abnormal peripheral clock genes circadian rhythm (73, 81) | |
| HD | <ul style="list-style-type: none"> • Delayed phase of the rest–activity rhythm (88) • Abnormal melatonin circadian rhythm (89) • Sleep fragmentation with night-time awakenings and reduced sleep efficiency (90, 91) | |

AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington's disease; IV, intra-daily variability; IS, inter-daily stability; RA, relative amplitude; BP, blood pressure; HR, heart rate.

of circadian HR variability (77, 78). However, these abnormalities can be influenced also by neurodegenerative changes of the autonomic nervous system documented in PD (79).

- (4) Abnormal temperature (80) and cortisol rhythm (73).
- (5) Abnormal clock gene rhythmicity in peripheral blood cells (73, 81).
- (6) Circadian fluctuations of motor symptoms (82) with a worsening of motor functions possibly related to the dopamine level variations over the day.

Interestingly, at difference with AD, where neuropathological hallmarks of pathology such as amyloid plaques and neurofibrillary tangles are described in the SCN of the hypothalamus, the neurodegenerative changes characteristics of PD, such as synuclein deposition and Lewy bodies, are not reported in the SCN. This suggests that in PD, the circadian imbalance, at least in the early phase, is not primarily due to a master clock pathology (6). This is consistent with the finding that PD patients in the early stage of the disease do not exhibit frank circadian rhythm abnormalities, such as for melatonin and other hormones (6, 83). It is not clear, based on the currently available evidences, if circadian misalignment occurs as an independent hallmark of PD pathology or can be interpreted as a consequence of many other non-motor manifestations of PD, such as sleep, cognitive, and behavioral problems. Moreover, the investigation of circadian dysfunction in PD is hampered by the possible influence of many confounding factors, such as the motor fluctuations intrinsic to the disease and the influence of L-DOPA therapy. However, the presence of circadian imbalance in PD is well supported by circadian abnormalities described in many animal models of PD [for a review, see Ref. (79)].

In this complex scenario, a possible role in the pathogenesis of circadian problems described in PD patients can also involve

the eye, and in particular the mRGC system. At this regard, there is documentation of a strict interaction between the mRGCs and the dopaminergic amacrine cells (84), a depletion of dopamine levels, and a specific synuclein deposition, particularly in the inner retina (39, 51, 52). Furthermore, a possible direct link between the eye, through the regulation of the melatonin synthesis, and the motor symptoms of PD has been postulated by Willis (85), as supported by the amelioration of motor symptoms after light exposure in PD patients (86). A summary of the main circadian abnormalities in PD is reported in **Table 1**.

In this wide scenario, it is possible that many factors, including the influence of mRGCs on modulating circadian rhythms and sleep, may play a role in the pathogenesis of circadian and sleep problems in PD. A more detailed investigation of this system is warranted, especially in *de novo* PD cases to elucidating the mechanisms behind.

BEYOND AD AND PD: HUNTINGTON'S DISEASE

Sleep and circadian dysfunction occur early in the disease course of Huntington's disease (HD) representing relevant non-motor symptoms of the disease [for a review, see Ref. (87)]. In particular, a delayed phase of rest-activity rhythm (88), an abnormal day-night ratio and melatonin rhythm (89), and consistent sleep fragmentation (90, 91) with increasing awakenings and reduced sleep efficiency have all been reported in HD.

Interestingly, the occurrence of sleep fragmentation and circadian misalignment in HD patients is relevant for aggravating the motor and cognitive problems of HD patients and bright light therapy improves motor and cognitive deficits in HD (90, 92). Moreover, even if there are evidences of neurodegenerative changes affecting the SCN in HD postmortem brain, the intact function of isolated SCN cells does not point to a primary central clock problem in the pathogenesis of circadian problems in HD, but more probably to a dysfunctional circuitry (87). Circadian abnormalities are also reported as early and prominent signs in the HD mouse models, the transgenic R6/2 and "knock-in" Q175 mice (93, 94). A summary of circadian abnormalities in HD is reported in **Table 1**.

Results on the possible occurrence of retinal degeneration in HD are contrasting, with some papers reporting the absence of retinal degeneration such as in the R6/2 mouse model (95) and others showing the presence of optic nerve degeneration (96, 97). In particular, a recent OCT study demonstrated the presence of temporal thinning in HD patients, which correlated with disease duration (97), with a pattern similar to PD and mitochondrial disorders (46, 47).

Interestingly, a recent study reported the occurrence of pupillary light response (PLR) dysfunction in R6/2 and Q175 mouse models, with a prevalent contribution of cone dysfunction in young-middle-aged mice and of mRGCs in old mice (98). In fact, a reduced PLR response is documented at low and moderate light intensity in young-middle-aged mice, whereas it is visible also at bright light in old mice, pointing to mRGC dysfunction. However, even if a significant reduction of melanopsin expression is evident in both mouse models also at early stages of the

disease, the mRGCs are morphologically intact and do not show any signs of neurodegeneration. In particular, the aggregation of huntingtin protein is evident in a significant amount in the retina and in particular in the RGCs, but it is not recognized in the mRGCs except for the old animals, suggesting that mRGCs are relatively spared by neurodegeneration (98). These findings are in line with the findings in mitochondrial optic neuropathies, i.e., Leber's hereditary optic neuropathy and dominant optic atrophy (DOA), where we demonstrated a relative resistance of mRGCs to mitochondrial dysfunction (99) and relative sparing of the PLR (100). This similarity can be explained by the significant contribution of mitochondrial dysfunction in HD pathogenesis (101, 102), including the mitochondrial dynamics alterations seen in HD, in particular increased mitochondrial fission (103), similar to DOA due to OPA1 mutations where fusion is affected (104).

However, even if the mRGCs are more resistant to neurodegenerative changes occurring in HD, the evidence of retinal pathology and, in particular, of reduced melanopsin expression in the retina of these mice can be relevant to the pathogenesis of circadian dysfunction in HD. These findings in HD are further examples that link the eye to the brain in a continuous dialog.

CONCLUDING REMARKS

In this review, we summarized the recent findings of optic nerve pathology and its possible link with circadian dysfunction in AD (4, 20, 105, 106), PD (5, 44), and HD (87, 96–98) focusing in particular on the possible role of mRGCs in the pathogenesis of circadian dysfunction in these neurodegenerative disorders.

We also underscore the differences in the patterns of optic nerve degeneration described in these disorders, which predominantly affect the magnocellular RGCs of the retina in AD (16, 21) and the parvocellular RGCs in PD (44, 46, 49) and HD (97), possibly explained by the predominant mitochondrial dysfunction documented in PD and HD. Similarities and differences are also discussed in regards to the circadian rhythm imbalance documented in AD and PD.

The presence of neuropathological hallmarks, i.e., β -amyloid plaques (30, 107, 108), α -synuclein (51, 52), and huntingtin (98) in the retina of these neurodegenerative disorders demonstrates that the retina is specifically affected by neurodegeneration and affords access to potential biomarkers of the disease.

AUTHOR CONTRIBUTIONS

CLM was responsible for conception, design, drafting, and revision of the manuscript. FR-C, AS, and VC were responsible for conception and revision of the manuscript.

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